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ORIGINAL ARTICLE

Potential role of age, sex, body mass index and pain to identify patients with knee osteoarthritis

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Abstract

Aim: To evaluate the potential role of age, sex, body mass index (BMI), radiographic features and pain in knee osteoarthritis (OA) case ascertainment.

Methods: A cross-sectional study was performed using information from the EPIPorto cohort; social, demographic, behavioral and clinical data was obtained. Pain was assessed using a pain frequency score (regarding ever having knee pain, pain in the last year, in the last 6 months and in the last month). Knee radiographs were classified using the Kellgren–Lawrence scale (0–4). Path analysis was used to assess the plausibility of the causal assumptions and a classification tree to identify characteristics that could improve the identification of patients with radiographic OA.

Results: Higher age and higher BMI were associated with higher radiographic score, but sex had no statistical association. Females, higher age, higher BMI and higher radiographic score were statistically associated with higher pain scores. For both genders, the classification tree estimated age as the first variable to identify individuals with knee radiographic features. In females older than 56 years, pain frequency score is the second discriminator characteristic, followed by age (> 65 years) and (BMI > 30 kg/m^2). Higher pain frequency and BMI > 29 kg/m^2 were relevant for identifying OA in men with ages between 43.5 and 55.5 years.

Conclusions: Age, BMI and pain frequency are independently associated with radiographic OA and the use of information on these characteristics can improve the identification of patients with knee OA. Beyond age, pain complaints are particularly relevant but the level of pain is different by sex.

Key words: clinical aspects, decision analysis, knee osteoarthritis, pain, radiography.

INTRODUCTION

Osteoarthritis (OA) is the most common form of joint disease[1–3] and one of the most important causes of pain and disability worldwide.[4] Thus, the need to improve case ascertainment and early disease identification is a priority in order to allow clinical and public health measures to be taken.

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OA can be defined as a multifactorial condition of joint failure mainly characterized by articular cartilage loss and subchondral bone sclerosis.[5] OA case ascertainment is normally based on pathological changes seen on X-ray and the presence of joint signs and symptoms.[6] Gradual radiographic evidence of joint damage and an increase in the amount of pain and physical disability are indicators of OA progression.[7] However, an accurate evaluation is difficult because of the non-specific nature of OA signs and symptoms[8,9] and sometimes their poor association with radiographic findings,[10] enhancing the need to find clinical and demographic characteristics that can be used in clinical practice to identify persons with this condition.

Among the most common joint sites affected by OA, the knee is one of the most prevalent[1] and more frequently associated with pain and disability.[11,12] The understanding of the pathophysiology of joint degeneration that leads to knee OA has been improving and different non-modifiable and modifiable risk factors have been identified.[11,13–15] Older age, female sex and higher body mass index (BMI) are established risk factors in knee OA, both as determinants and as key factors on disease progression.[16–18] However, the potential role of a formal inclusion of such factors to improve the ability to identify patients with knee radiographic OA is not so well understood.[19–21] Identifying simple clinical and demographic characteristics that can represent a high probability of having radiographic OA is useful, particularly in situations where radiography might be difficult, undesirable, or even to decide if it is necessary. On the other hand, as OA-related pain is the reason that most often leads to the demand for health care, it is important to understand how these characteristics are related, and can contribute to an early identification of patients.

The purpose of this study is to evaluate the role of pain, together with age, sex and BMI, in the identification of patients with knee radiographic OA.

MATERIALS AND METHODS

Data collection

The study was performed using information collected as part of the *EPIPorto* cohort.[22] Briefly, this cohort evaluates non-institutionalized adults, resident in Porto, an urban centre located in northwest Portugal with almost 400 000 inhabitants. Participants were selected by random digit dialling and invited to visit the University of Porto Medical School for an evaluation, which included an interview based on a structured questionnaire on social, demographic, behavioral and clinical data. The proportion of participation was 70%. The local ethics committee of S. João Hospital, a university hospital, approved the study protocol. All participants gave written consent to participate in the study, which was carried out in accordance with the Helsinki Declaration.

Data were collected by trained interviewers using structured questionnaires. We evaluated marital status (categorized into either married/civil union and single/divorced/widow), years of education (measured as the number of successfully completed years of formal schooling), occupation (white collar, blue collar and others, including students, unemployed and those who never had a job) and current occupational status (working, retired and others). A previous medical diagnosis of chronic diseases in general and of knee OA was evaluated by self-reported information.

Frequency of knee pain was evaluated using a set of 'yes/no' questions. First, participants were asked if they 'ever had knee pain not related with any trauma or injury?' If participants gave a positive answer to this question they were asked to answer (yes/no) to three further questions: 'In the last year did you have more than 3 knee pain episodes?'; 'During the last 6 months did knee pain last longer than a week?'; and 'During the last month did you have knee pain?' To understand if these questions could be used to measure the frequency of knee pain, factor analysis for dichotomous variables was performed. Pain intensity was also measured using the Visual Analogue Pain Scale (VAS) (0–100 mm)[23] in the different time frames evaluated by the questions (at the moment, in the last year, in the last 6 months and in the last month).

Body weight was measured to the nearest 0.1 kg using a digital scale (SECA®) and height was measured to the nearest centimeter using a wall-stadiometer (SECA®); then using BMI (weight [kg]/height [m^2]) we classified participants into three categories (< 25.0 kg/m^2 underweight or normal; 25.0–29.9 kg/m^2 overweight; ≥ 30 kg/m^2 obese).[24]

Weight-bearing antero-posterior[19] and lateral, semi-flexed (45° flexion)[25] radiographs of knees were obtained. Radiographic knee OA was evaluated in tibio-femoral (medial and lateral) and patello-femoral compartments of the right and left knee, and graded according to the Kellgren–Lawrence scale (KL:[5] Grade 0, none, no visible features of OA; Grade 1, doubtful, questionable osteophytes or questionable joint space narrowing; Grade 2, minimal, definitive small osteophytes, little/mild joint space narrowing; Grade 3, moderate, definitive moderate osteophytes, joint space narrowing of at least 50%; Grade 4, severe, joint space impaired severely, cysts and sclerosis of subchondral bone.[26,27] Radiographs were scored only by one reader, although he was unaware of the participants' clinical data.

Participants

From the 2485 participants of the *EPIPorto* cohort that participated at the baseline evaluation, 1682 were re-evaluated during the follow-up performed between 2005 and 2008. From those, the first 1000 were systematically invited to have knee radiographs and 907 were evaluated; from these 13 participants had unreadable or incomplete knee radiographic evaluation. The final sample comprised the 894 participants with complete data on knee OA.

Data analysis

Quantitative variables were described by mean (standard deviation) and qualitative variables were described by absolute and relative frequency.

The mean comparisons were made using independent samples *t*-test or Mann–Whitney *U* test for skewed distributions and the proportion comparisons were made using the Chi-square test.

Principal components analysis and factor analysis for dichotomous variables (latent trait model) were used to evaluate the dimensionality of radiographic knee OA (in order to identify the best way to summarize radiographic lesions) and in the pain questions (to measure the frequency of knee pain), respectively. The internal consistency of both was assessed by Cronbach's alpha.

Pain questions were considered as a score for knee pain, with an increase in score representing an increase in pain frequency. Score –1 represents participants with no knee pain; score 0 represents those that reported 'ever had knee pain' but reported no pain in the last year; participants were scored from 1 to 3, according to the number of positive answers regarding 'the last year', 'the last 6 months' and 'the last month'. Path analysis was used to evaluate the role of gender, BMI and age in pain frequency and radiographic scores. Path analysis is an extension of regression analysis which allows for simultaneous estimation of the interrelations between variables in a set.[28] This technique is being increasingly used to deconstruct and compare the magnitudes of effects between variables with complex interrelations or to test the plausibility of mediation effects.[29] Path analysis was fitted with Mplus software (Muthén and Muthén, Los Angeles, CA, USA). The association between age, sex, BMI, pain frequency and radiographic scores were estimated by correlation coefficients and respective 95% confidence intervals. Goodness of fit was evaluated using χ^2 for model fit, comparative fit index, Tucker–Lewis Index, root mean square error of approximation and square root mean residual according to the Akaike and Bayesian criteria.[28] Radiographic scores used in the path analyses were computed by the numeric mean of the scores of each of the six joint compartments evaluated.

A decision tree to estimate radiographic knee OA was constructed separately by sex using all variables that had shown to have a direct or indirect effect on path analyses. The radiographic score equal to 2 or more in at least one of the six joint compartments evaluated (having radiographic knee OA) was our major outcome. The Rpart and Ltm pakages from *R* ®, a language and environment for statistical computing, were used to estimate the decision tree and the latent trait model.[28]

RESULTS

Our sample was composed mainly of females (59.2%); the overall mean (standard deviation) age was 58.1 (14.2) years. Knee pain 'ever having knee pain not related with any trauma or injury' was reported by 43.8% of participants and knee radiographic OA (KL $\geq$ 2) was present in 46.2%. There was a significantly lower proportion of females, a significantly higher proportion of overweight/obese individuals and lower education levels among the included participants compared to those who were not included in this analysis (Table 1).

A principal component analysis considering all the joint compartments evaluated was performed in order to test if the mean score of all knee radiographs evaluated was a good summary measure to describe radiographic OA features. This analysis allowed us to identify only one component for knee radiographic OA features, that explained 67.0% of the variance and a Cronbach's alpha of 0.90 (Table 2). So, we estimated a mean score based on all joint compartments of left and right knees.

Factor analysis was used to understand how to summarize the data obtained in the knee pain frequency questions (dichotomous variables): it identified only one factor and all items showed a factor loading higher than 0.86, with a global Cronbach's alpha of 0.70 (Table 2).

Figure 1 presents the causal pathways assumed for testing the relations between age, sex, BMI, radiographic score and pain frequency score that allowed us to obtain a summary model of these relations: χ^2 for model fit was 0.02 ($P = 0.88$); comparative fit index = 1.00, Tucker–Lewis Index = 1.02, root mean square error of approximation < 0.01 and square root mean residual < 0.01. Association between variables was described by correlation coefficients (95% confidence intervals). Age and BMI were used as continuous variables in the path analysis which then provided the cut-off values described in Fig. 1. We observed no effect of sex on radiographic lesions, but age and BMI were

Table 1 Comparison between included and excluded participants

	Excluded n = 788	Evaluated n = 894	*P*-value
Age (years), mean (SD)	56.7 (15.4)	58.1 (14.2)	0.05
Sex, *n* (%)			
Women	518 (65.7)	529 (59.2)	< 0.01
Marital status, *n* (%)			
Married	523 (66.4)	611 (68.3)	0.75
Single or divorced	265 (33.6)	283 (31.7)	
Years of education, *n* (%)			
0–4 years	279 (35.4)	330 (37.0)	< 0.01
5–9 years	140 (17.8)	224 (25.1)	
10–12 years	127 (16.1)	123 (13.8)	
≥ 12 years	242 (30.7)	216 (24.2)	
Occupation, *n* (%)			
White collar occupations	468 (59.4)	530 (59.4)	0.39
Blue collar occupations	248 (31.5)	264 (29.6)	
Others (unemployed, student, never had a job)	72 (9.1)	98 (11.0)	
Current occupation status, *n* (%)			
Working	344 (43.7)	357 (40.0)	0.14
Retired	333 (42.3)	383 (42.9)	
Others (unemployed, student, never had a job)	111 (14.1)	153 (17.1)	
Self-reported diagnosis of knee OA, *n* (%)			
Yes	109 (13.9)	144 (16.1)	0.11
Other chronic disease, *n* (%)			
Yes	539 (69.5)	590 (66.4)	0.10
Height (cm), mean (SD)	160.00 (9.08)	160.47 (9.22)	0.29
Weight (kg), mean (SD)	70.01 (28.71)	70.42 (13.33)	0.70
Body mass index (kg/m^2), *n* (%)			
< 25.0 kg/m^2	293 (37.8)	273 (31.0)	0.01
25.0–29.9 kg/m^2	297 (38.3)	382 (43.4)	
≥ 30.0 kg/m^2	186 (24.0)	226 (24.9)	
Knee pain 'ever'			
Yes	315 (40.2)	391 (43.8)	0.14

OA, osteoarthritis; SD, standard deviation.

positively associated with higher radiographic score. Regarding pain frequency score, we found a direct and positive effect from radiographic score, showing that pain is in part explained by OA radiographic features. However, pain frequency score is also explained by sex (lower pain scores were reported by males), by BMI (higher BMI is associated with higher pain score) and, although with a small association, by age (higher age contributed to higher pain score).

Table 2 Principal component analysis for knee radiographic features and internal consistency/factor analysis for dichotomous variables (latent trait model) for knee pain questions

Radiographic features	Component 1	% of variance explained	Global Cronbach's alpha
Right knee medial tibio-femoral OA	0.84	67.0%	0.90
Left knee medial tibio-femoral OA	0.82		
Right knee lateral tibio-femoral OA	0.80		
Left knee lateral tibio-femoral OA	0.83		
Right knee patello-femoral OA	0.82		
Left knee patello-femoral OA	0.81		
Pain questions	**Factor loading**	**Cronbach's alpha If item deleted**	**Global Cronbach's alpha**
'In the last year did you had more than three knee pain episodes?'	0.97	0.51	0.70
'During the last 6 months did knee pain last longer than a week?'	0.86	0.74	
'During the last month did you have knee pain?'	0.95	0.52	

OA, osteoarthritis.

For both genders the classification tree identified age, BMI and pain frequency as relevant variables to identify participants with radiographic OA (radiographic score equal to 2 or more, in at least one joint compartment). For females (Fig. 2), among those aged ≥ 56.5 years the presence of pain is a major predictor of radiographic OA (more than 80%). In the absence of pain, having more than 65.5 years or a BMI ≥ 30.5 kg/m^2 can predict an increased likelihood of having OA. This classification tree model presented an acceptable goodness of fit based on receiver operating characteristic (ROC) of 0.73, sensitivity (80%), specificity (67%), positive predictive value (77%) and negative predictive value (71%).

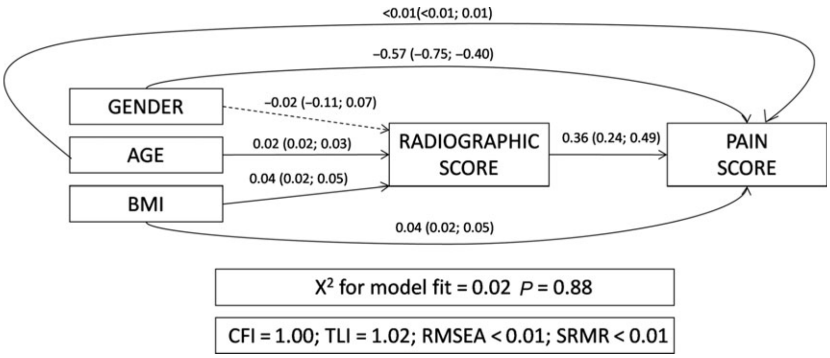

Figure 1 Path analysis between sex, age, BMI (body mass index), radiographic score and pain frequency score.

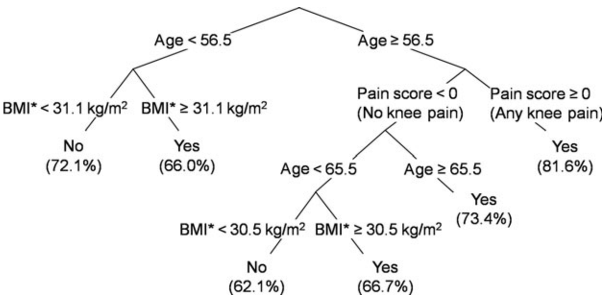

Figure 2 Classification tree for the prediction of radiographic osteoarthritis (OA) in females. BMI, body mass index.

For males (Fig. 3), the first predictor was age $\geq$ 55.5 years. Among males aged $\geq$4 3.5 and < 55.5 years, having pain complaints in the last year, month or week (pain frequency score $\geq$ 1.5) or a BMI $\geq$ 29.3 kg/m^2 represents an increased likelihood of having OA. The ROC was 0.70, with a higher sensitivity (88%) but a lower specificity (52%) compared with the model for females. Positive predictive value and negative predictive value were, respectively, 72% and 76%.

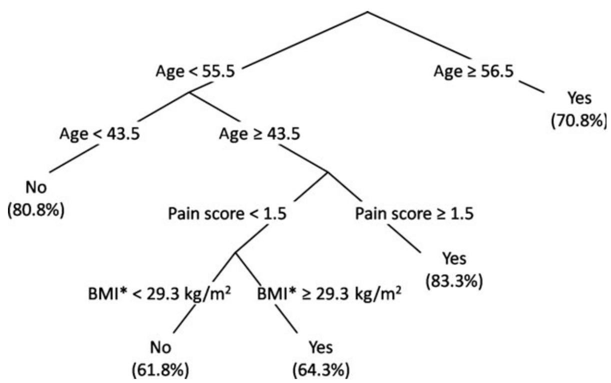

Figure 3 Classification tree for the prediction of radiographic osteoarthritis (OA) in males. BMI, body mass index.

DISCUSSION

Although OA risk factors have been extensively studied worldwide, it is important to understand the role of age, sex, BMI and pain in the probability of having radiographic OA. Simple variables can allow predicting the need to perform a radiographic exam or, when it is not possible, they can help to understand which radiographic findings can be expected.

In both clinical practice and in the research setting the measurement of OA-related pain is a challenge.[30,31] Our previous work[32] showed that two of the questions presented a high sensitivity but a low specificity but when we considered all of them, there was a slight increase in the ability to identify participants with radiographic KL $\geq$ 2.

This reduced ability to identify participants with OA based on pain complaints, is in accordance with a meta-analysis which found that a higher number of questions related to pain allowed improved sensitivity but implied a large restriction of specificity.[33]

Our pain frequency score was based in a small number of questions, with any hierarchy on complaints, created by a group of health professionals with field clinical expertise and that could be easily used in a clinical setting or in population-based studies. It showed an acceptable performance (in terms of the internal consistency of the three items associated with pain frequency score) allowing us to assume it as a good measure. The use of this score allowed us to have an easy summary measure of pain and to order pain complaints instead of a dichotomous approach (pain present or absent) that was unable to take in account the complexity of pain complaints. As previously reported,[32] higher discriminatory ability to identify participants with radiographic OA was found using the pain frequency score compared with single questions on knee pain.

Pain intensity may also be an important aspect in OA case ascertainment.[19] We tried to use pain intensity assessment, obtained through the visual analogue pain scale, but this information did not improve our model for the prediction of knee radiographic OA (even when we used data specific for each of the time periods evaluated). Furthermore, our decision tree statistical criteria did not include these variables as relevant to explaining radiographic OA features and identified the pain score without the pain quantification as the most relevant variable; the best model fit was obtained only with pain frequency data and therefore data for pain intensity was not considered in our model.

Some of the radiographic and pain discordance in knee OA may be in part related to the fluctuating nature of knee pain.[34] Pain questions did not evaluate the mechanical component of pain that is an important aspect in OA. Also, the recall bias in pain assessment can be a limitation, especially since episodes that occurred over time, or are less serious, were less likely to be remembered.

The differences in the associations between radiographic and outcome measures might also be related to the radiographic views and classification used.[35] It is known that multiple views detect more radiographic OA changes than single views alone[36] and weight-bearing antero-posterior and lateral radiographs may not be sufficient to show the true extent of the pathology.[37] Moreover, the radiographic evaluation according to the KL score of 2–4 has some known limitations.[26,36,38] Nevertheless, the radiographic views selected are frequently used[35] and no important bias is expected in our OA classification of radiographs, since they were scored only by one reader that was blinded to all clinical data of the participant.

We used a mean radiographic score (evaluating all joint compartments of the left and right knees) and we considered a participant with a score ≥ 2 has having radiographic OA. Although we performed a principal component analysis this measure of radiographic features has not been validated and this can be a study limitation.

Path analysis was used as an approach to understand the mechanisms beyond individual risk factors, radiographic features and complaints of pain.[29] Our model showed good fitting parameters and identified that higher age and higher BMI were associated with higher radiographic score. This is in accordance with previous studies that identified these aspects as important determinants of knee OA occurrence and progression.[11,13]

Age is a strong predictor of OA development.[39] The vulnerabilities of a joint that occur as part of the aging process make it susceptible to disease;[40] diminished capacity for cartilage repair, hormonal changes and the cumulative effects of environmental exposures are possible age-related mechanisms.[41]

Higher BMI is known as one of the most important risk factors for knee OA[12,17,42] and is a predictor of OA progression.[3] Overweight and obesity associated with OA is probably the result of a mechanical process with an increased of load and stress for the joints;[11,42,43] another possible explanation is associated with the pro-inflammatory action of fat.[44,45] Furthermore, the majority of people with OA have at least one co-morbid condition[46] and higher age and higher BMI increases the prevalence of multiple co-morbid conditions which in turn increases the impact of OA.[1]

Even though some theoretical pathophysiological mechanisms can be proposed to explain sex differences on the incidence of OA,[7,11] and several studies have found that females may have higher risks of development and progression than males,[13,47,48] our path analysis did not find a statistical association between gender and radiographic scores. However, it is possible that the higher incidence of OA found in females by population studies can be explained more by a higher probability of complaints reported by females, and therefore an increase the likelihood of diagnosis, rather than by a real gender differences in the occurrence of OA.[6,19]

As far as pain frequency score is concerned, we found that more severe radiographic features presented a strong association with higher pain scores. This supports the relevance of pain as an important marker of OA and is in accordance with data showing that pain is frequently the primary reason for seeking health care.[1,42] Nevertheless, pain is highly associated with physical and psycho-social aspects besides pathological changes and this can explain the high variability of results found in the literature,[49] notwithstanding our results reinforcing the need to measure and understand pain complaints, especially in younger people.

Although radiographic features are a useful objective marker of OA, this information alone has limited clinical value[36] and needs to be understood in the context of other clinical signs. On the other hand, it is important to understand that several variables can predict a positive radiographic evaluation in OA. These characteristics may represent a high probability of radiographic OA and can be used in clinical practice to identify persons with the condition, particularly in situations where radiography is not available. Based on the classification tree, age was the first variable that identified individuals with radiographic features ($\geq$ 56.5 years) in both genders. In females older than 56 years, pain frequency score is the second discriminator characteristic, followed by age (> 65) and (BMI (> 30 kg/m^2). Pain frequency score ≥ 1.5 and BMI > 29 kg/m^2 were relevant for identifying OA in men with ages between 43.5 and 55.5 years. This was in accordance with the previous associations found in our path analysis and in accordance with established guidelines[33,50] that include the need to consider radiographic findings in accordance with age, BMI and pain for a correct OA case ascertainment and management. Overall, the analysis that we present, allowed us to identify cut-offs for each of these widely known characteristics that can be used according to the set of patient characteristics.

Our results need to be understood remembering that several other factors play an important role in OA development. Biomechanical factors can also contribute to OA, such as, for example, malaligned joints, proprioceptive deficits and muscle weakness;[19] other systemic factors such as pre- and post-menopausal status in women[51] could also influence OA. These aspects, not evaluated in this study, should be part of a more comprehensive study in the future.

The major limitation of this study is its cross-sectional design, which does not allow the exploration of how observed differences have been developed and interact over time; however, since we are estimating the probability of having radiographic OA changes, this aspect does not have a relevant effect.

Although our study was developed from a population-based study, and the differences between excluded and included are slight, losses of follow-up may cause selection bias which could limit the generalizability of these results. Moreover, the interpretation of the results of our model should be made taking into concern the low specificity found in males.

In clinical practice, understanding simple clinical variables can improve OA case ascertainment and early disease identification. Although our study has limitations, our results can aid the clinician to understand how to deal with age, sex, BMI and pain in the identification of knee OA patients. Due to the fact that the present study has only analyzed data from knee joints, the implication of these results on patients with OA in other joint sites is limited.

In conclusion, we identified that in knee OA, older age and higher BMI were associated with higher radiographic score, but sex had no statistical association. Females, higher age, higher BMI and higher radiographic score were statistically associated with higher pain scores. Although pain complaints are also dependent on sex and BMI, its measurement is useful to identify patients with radiographic OA, particularly in younger non-obese individuals.

DISCLOSURES

No further contributions or research funding sources need to be reported. The authors declare that they have no conflict of interests.

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